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Automated video analysis of age-related motor deficits in monkeys using EthoVision

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Abstract

Previous studies comparing age-related changes in locomotor function in nonhuman primates have generally relied on subjective human observations or rudimentary infrared motion sensors. Here, we used the automated video-tracking system EthoVision to objectively quantify locomotor activity in 6 young, 6 middle-aged and 12 aged female rhesus monkeys. The video records were analyzed for distance traveled, movement speed and vertical activity. Our results showed that the young monkeys (4.9 ± 0.1 years old) traveled twice the distance and moved 48% faster than the middle-aged monkeys (15.7 ± 0.5 years old), and traveled thrice the distance and moved 67% faster than the aged monkeys (26.3 ± 0.9 years old). In addition, young monkeys were vertically more active (20/60 min) than both the middle-aged (7/60 min) and the aged (1/60 min) monkeys. Furthermore, the locomotor performance of the individual animals significantly correlated with increasing age for all three measures. We conclude that EthoVision is a reliable and objective tracking method for detecting age-related differences in locomotor movements in rhesus macaques, and possibly in humans.

Keywords: Aging; Motor functions; Nonhuman primates; Rhesus; Video-tracking

1. Introduction

In correspondence with human aging [36], we have previously demonstrated that age-related decline in fine hand motor performance can be detected objectively in rhesus macaques using an automated food-retrieval task [10,42]. In addition, only a few studies have shown that as rhesus monkeys age, they often exhibit two or more parkinsonian signs and display whole body movement dysfunctions similar to that of aged humans as indicated by decreased home-cage activity levels [8,19,33,42]. However, those studies were dependent either on human observations or rudimentary infrared motion sensors, or both. These methods are not only limited in their range of applicability, but also in the range of behavioral measures that can be collected. For instance, human observations of animal behavior and manual data collection can be influenced by the subjective bias of the observer or fatigue, while activity cages equipped with photocells can only have a limited number of infrared motion sensors, so that locomotor activities are invariably missed during data acquisition due to low spatial resolution. Moreover, precise recording and analysis of an animal's path is not possible with these methods.

Recently, automated video-tracking systems have enabled researchers to study locomotor activity in animals more reliably than if they are manually recorded. Automated observation using video-tracking is particularly suitable for measuring locomotor behavior expressed as spatial measurements such as distance traveled or movement speed, that are difficult for the human observer to accurately quantify. Various automated methods, mostly prototypes, have been used to study animal behavior in recent years [7,18,21,35,41]. The commercially available video-tracking system, EthoVision, is a specific example of such systems. This automated

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image processing system was designed as a general-purpose video-tracking movement analysis, and behavior recognition system [32].

While the majority of studies using EthoVision have been conducted in rats and mice [17,34,37], it has also been used in research to successfully study other species including insects, marine invertebrates, fish and farm animals [27,38,39]. However, to our knowledge, this automated system has not been tested to study age-related motoric changes in nonhuman primates. Thus, the current study was designed to investigate whether the EthoVision system can be used to objectively quantify age-related differences in whole body movements in nonhuman primates by comparing measures of distance traveled, movement speed and vertical activity between groups of young, middle-aged, and aged female rhesus macaques.

2. Methods

2.1. Animals

Twenty-four female rhesus monkeys (*Macaca mulatta*) obtained from a commercial supplier (Covance, Alice, TX) were used in this study. Six were young adults ranging from 4 to 5 years old (mean age = 4.9 ± 0.1 years), 6 were middle-aged ranging from 14 to 18 years old (mean age = 15.7 ± 0.5 years) and 12 were aged adults ranging from 24 to 33 years old (mean age = 26.3 ± 0.9 years). The animals were maintained on a 12-h light/12-h dark cycle and housed in individual cages in the vivarium of the University of Kentucky. Their diet consisted of certified primate biscuits in the morning supplemented daily in the afternoon with fresh fruit or vegetables, and water was available ad libitum.

2.2. Videotaping procedures

Prior to being videotaped, the animals were transported to an adjacent room and transferred to specially-designed cages and given 2 h to adapt. The videotaping cages measure 28 in. wide × 32 in. high × 32 in. deep, have a white background wall and a clear Lexan window permitting videotaping. Each videotaping cage is illuminated by two 48 in. long fluorescent lights located 30 in. above the cage. Videotaping occurred in the afternoon between 1 and 2 p.m. Beginning at 1 p.m., a technician entered the room to start recording the session after placing food items (marshmallows or small pieces of fruit) on the ledge of the cage to elicit the animal to stand-up, reach out for the food and move about the cage. Then, the technician left the room and the animals were videotaped for a single 60-min session with no one in the room. The locomotor activity of each animal was recorded by a SONY Handycam Vision camera mounted on a stationery tripod. While water was provided ad libitum during videotaping, the animals were fed their fruit or vegetables after completion of data acquisition and upon return to their home-cage.

All procedures were conducted in the Laboratory Animal Facilities of the University of Kentucky, which are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Veterinarians skilled in the health care and maintenance of nonhuman primates supervised all animal care, and all protocols were approved by the University of Kentucky's Animal Care and Use Committee.

2.3. The EthoVision video-tracking system

Distance traveled (cm), movement speed (cm/s) and vertical activity (s) measures were quantified from 8-mm videotapes (SONY P6-120MPL) using the commercially available video-tracking system EthoVision Pro (version 2.3, Noldus Information Technology, Asheville, NC) coupled to a SONY Digital 8 video cassette recorder. The system runs on a Pentium based computer with a frame grabber card (PICOLO, Belgium), so that the analog video signal coming from the video cassette recorder is digitized and transferred to the computer.

A window on the computer screen directly displays the video image, and the boundaries within which tracking took place were defined by accurately tracing the outline of the cage in the video image. In addition, two zones were outlined, so that the overall activity measured in the entire cage could be analyzed in terms of vertical (top half) or horizontal (bottom half) activity. The animals were videotaped for a single 60-min session and the video-tracks were analyzed for each animal at a rate of 6-sample/s. For every sample, the cage was scanned and the position of the tracked animal was determined by using a gray scale detection method (brightness). This entails calibrating the software to distinguish the dark-colored animal from the background, which is then defined as all other pixels. The back wall of the cage was painted white to provide a background with a maximum degree of contrast with the dark-colored primate. This automated method relies on determining the position of the center of mass of the animal in the cage, and the resultant x–y coordinates extracted as a function of time are used for calculating the movement pattern during the observation period. These coordinates were subsequently related to actual spatial measures by calibrating the software to the dimension (width) of the cage, so that parameters such as distance traveled were calculated in centimeters instead of pixels. For additional details, see the review by Noldus and colleagues [32].

2.4. Statistics

For each measure, the group averages were analyzed for significant age-associated differences using a one-way analysis of variance followed by Newman–Keuls post hoc comparisons. In addition, regression analysis was used to further examine age-associated effects revealed initially by group comparisons. Linearity is reported as R^2 values. A p-value <0.05 was considered significant in all analyses.

3. Results

Based on factors such as age at puberty, longevity and brain parenchymal volume, 1 year of rhesus life equals approximately three human years [1,13,40]. The monkeys used in the present study ranged in age from 4 to 33 years old, and therefore, were roughly equivalent to 12–99 years old in human age.

Representative overall movement patterns measured by EthoVision are shown in Fig. 1 for a young monkey in panel A (#E058, age 5), for a middle-aged monkey in panel B (#H695, age 17), and for an aged monkey in panel C (#379P, age 26).

Overall distance measurements (cm) were taken from activity in the entire arena. As shown in panel A of Fig. 2, the young monkeys traveled a greater distance than both the middle-aged (2.5× as far) and the aged (3× as far) animals over the entire arena during the observation period. Although the average distance traveled by the middle-aged animals was greater than that of the aged animals, the difference was not statistically significant as there was some overlap between the two groups (see panel B). To further examine age-associated effects revealed initially by group comparisons, the data was fitted to a linear model using simple regression where X = age and Y = distance (cm) (Fig. 2, panel B). Data analysis revealed that the locomotor performance of the individual animals significantly correlated with increasing age for overall distance measurements ($R^2 = 0.54$, p-value < 0.0001, rate of decline in distance traveled = 643 cm/year).

Similar to overall distance traveled, movement speed measurements (cm/s) were taken from activity in the entire arena. As seen in panel A of Fig. 3, the movement speed of the young monkeys was significantly faster than that of both the middle-aged and the aged animals by 48 and 67%, respectively. While the average movement speed of the middle-aged animals was greater than that of the aged animals, the difference did not reach statistical significance as there was some overlap between the groups (see panel B). Simple linear regression analysis where X = age and Y = speed (cm/s) indicated that speed of movement significantly correlated with age ($R^2 = 0.53$, p-value < 0.0001, rate of decline in movement speed = 0.2 cm/s year) (Fig. 3, panel B).

In contrast to overall distance traveled and movement speed, vertical activity results (s) were based on measurements taken only in the upper half of the cage. Fig. 4 (panel A) illustrates the amount of time the animals were moving while in the top half of the cage, including walking upright and swinging from the cage bars. Unlike the measures of distance traveled and movement speed, both young and middle-aged animals spent significantly more time moving in the top half of the cage as compared to the aged animals. This is the only measurement for which a statistical difference was seen between the middle-aged and aged animals. The young animals were also significantly more active than the middle-aged animals. Indeed, the young animals were vertically active 20 of 60 min (33%) as compared to 7 of 60 min (12%) for the middle-aged and to less than 1 min (<2%) for the aged animals. Simple linear regression analysis where X = age and Y = time (s) indicated that vertical locomotor activity significantly correlated with age ($R^2 = 0.76$, p-value < 0.001, rate of decline in vertical activity = 47 s/year) (Fig. 4, panel B). This represents the best correlation of all three measures.

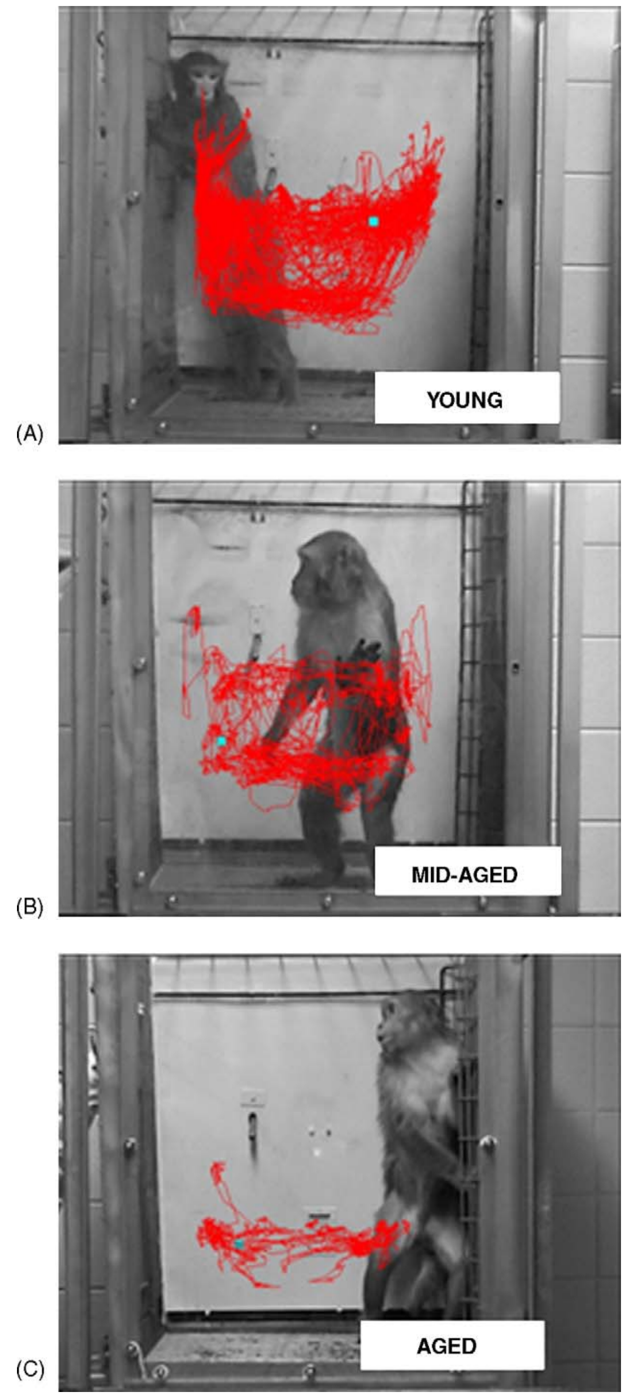

Fig. 1. Representative movement patterns obtained during a single 60-min observation period are shown for a young monkey in panel A (#E058, age 5), for a middle-aged monkey in panel B (#H695, age 17), and for an aged monkey in panel C (#379P, age 26).

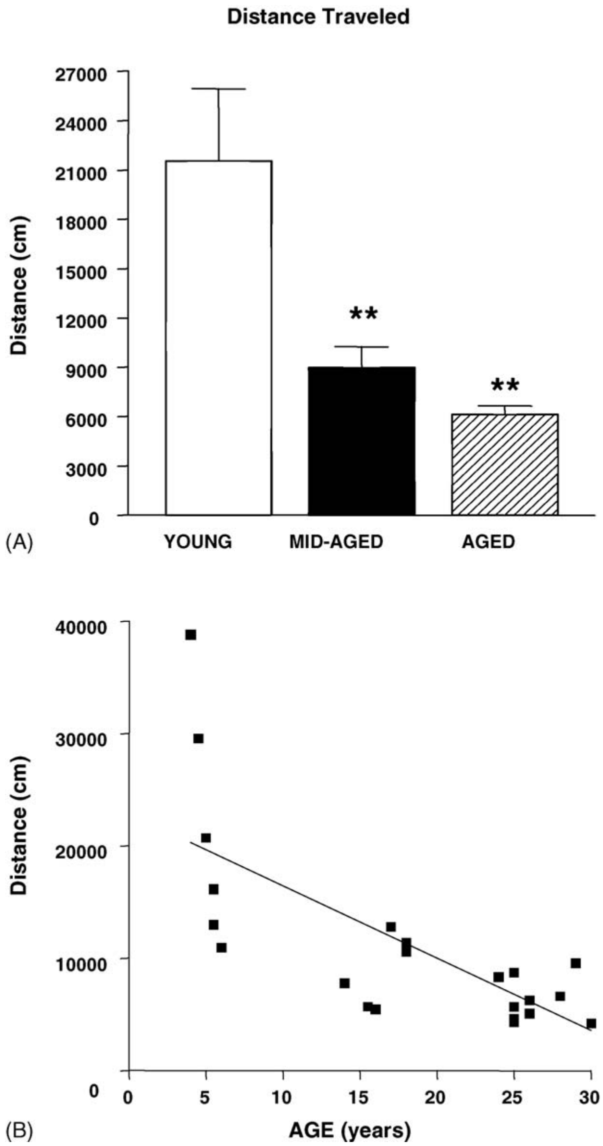

Fig. 2. Measurements of overall distance traveled (cm) were taken in the entire arena during a single 60-min observation period. As shown in panel A, the young animals traveled 2.5 times the distance of the middle-aged animals and 3 times the distance of the aged animals. Values are expressed as means ± S.E.M. ($^{**}p < 0.01$ vs. young group). Distance traveled also significantly correlated with age as seen in panel B ($R^2 = 0.54$, $R = 0.73$, $p < 0.0001$).

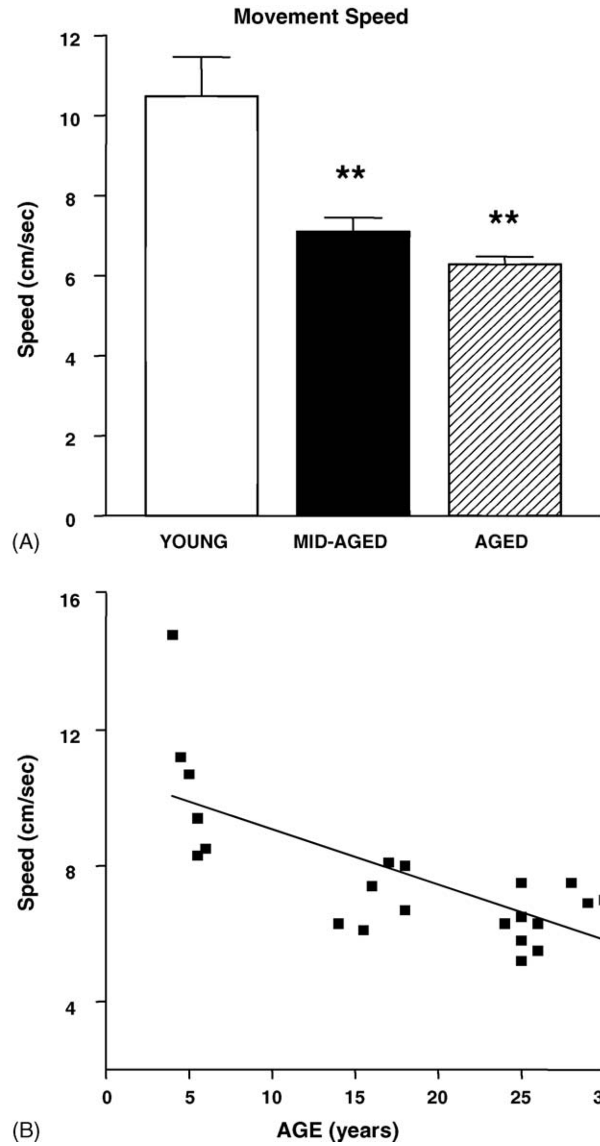

Fig. 3. Measurements of movement speed (cm/s) were taken in the entire arena during a single 60-min observation period. As shown in panel A, the young monkeys were significantly faster than both the middle-aged (48%) and the aged animals (67%). Values are expressed as means ± S.E.M. ($^{**}p < 0.01$ vs. young group). Speed of movement was significantly correlated with age as seen in panel B ($R^2 = 0.53$, $R = 0.73$, $p < 0.0001$).

4. Discussion

In the present study, we have used an automated pattern recognition software to analyze spatiotemporal measures of locomotor activity collected in 24 female rhesus monkeys ranging from 4 to 33 years of age. Our data demonstrate that the commercially available video-tracking system EthoVision Pro is sensitive enough to detect age-related declines in motor functions in non-human primates. When comparing young to middle-aged and aged rhesus monkeys, differences were seen in all three measurements of gross locomotor movement: distance traveled, movement speed, and vertical activity. The young monkeys were significantly faster (up to 67%) and covered more distance (up to three times) than both middle-aged and aged monkeys. In addition, young monkeys were vertically more active in the top half of the cage (climbing, swinging, etc.) than both middle-aged and aged monkeys, and in this particular measure, the middle-aged monkeys were also significantly more active than the aged animals. Finally, regression analysis indicated that the locomotor performance of the individual animals significantly correlated with increasing age for all three measures.

Studies conducted in several other species from invertebrate larvae to pigs have demonstrated EthoVision to be a

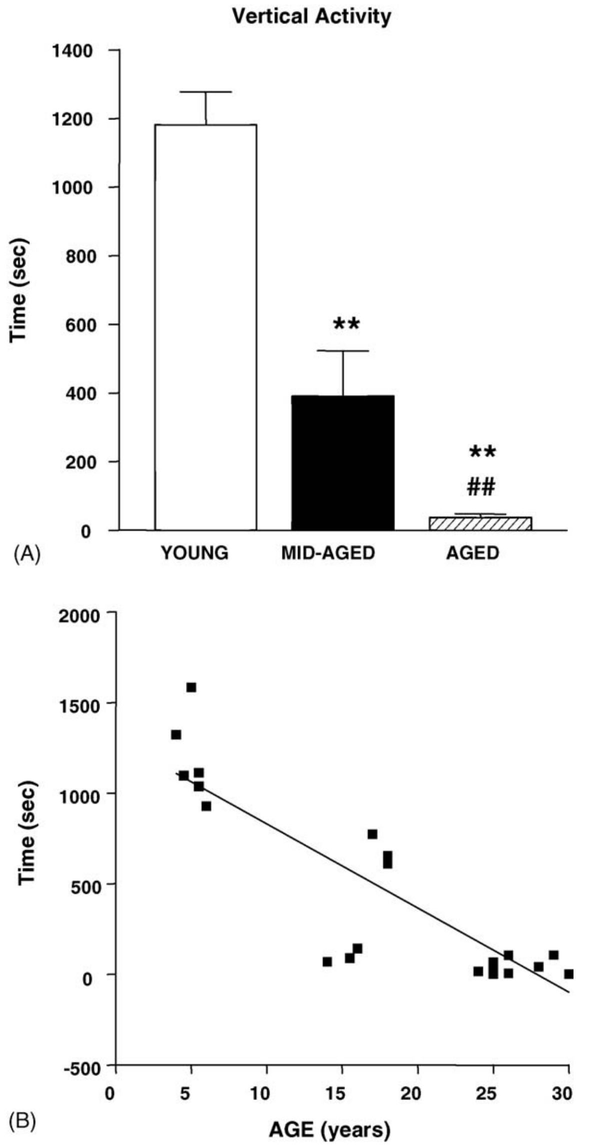

Fig. 4. Measurements of vertical activity (s) were taken in the top half of the arena during a single 60-min observation period. As shown in panel A, the young monkeys were significantly more active in the top portion of the cage than both the middle-aged and aged animals. This measurement also showed the middle-aged monkeys to be vertically more active than the aged animals. Values are expressed as means ± S.E.M. ($^{**}p < 0.01$ vs. young group, and $^{\#\#}p < 0.01$ vs. middle-aged group). Vertical activity was significantly correlated with age as seen in panel B ($R^2 = 0.76$, $R = 0.87$, $p < 0.0001$).

reliable tool for monitoring and measuring motor activity under a variety of conditions. The majority of those studies have used EthoVision to measure behavior in rats and mice in combination with the Morris water maze test, for spatial learning and changes in motor activity, and the open field test, for anxiety and social interactions [6,17,34]. EthoVision has also been used in larger mammals and farm animals as well. For instance, Sustr and colleagues [39] studied the spatial position of pigs during paired social interactions, while Bokkers and Koene [5] monitored the speed of chickens moving towards different diets to assess motivation and walking ability. In addition, the EthoVision software has been employed to track walking patterns and movement paths in ticks [24,38], locomotor activity and behavior in fish [3,4], and settlement behavior of the cypris larvae [27]. Other video-tracking systems besides EthoVision have also been used to monitor activity in several different species [22,31]. However, these devices were either prototypes or not commercially available and have not been used in aging research.

The use of EthoVision to determine age-related differences in motor functions is of particular advantage in that the software records and analyzes behaviors more accurately without the risk of observer fatigue. In addition, it is not necessary to have the same observer view all the videotapes to ensure equal and accurate measurements. However, although EthoVision is an objective measuring device of locomotor activity, human observation should not be ruled out completely when using this technology and instead should be viewed as a useful complement to data acquired from the EthoVision software system. Indeed, some of the limitations of EthoVision include the inability of the system to measure social behaviors such as grooming and some age-related deficits such as tremor or stooped posture. Therefore, it is necessary to have some human observation to verify and record certain behavioral activities. The video recording area and set up can contribute to some system limitations as well. Proper lighting, video background, camera set up, and characteristics of individual monkeys all influence the ability of the system to record movement accurately. In particular, we found that shadows cast in the cage area from the light source could cause interference when tracking the center of mass of dark-colored animals, making the calibration process more difficult.

Our findings are in line with those obtained in aged human subjects [36] and those previously obtained in non-human primates suggesting that locomotor activity decreases significantly with age [8,25,42]. Under the present experimental conditions, all the animals were transferred from their home-cages to specially designed videotaping cages and given 2 h to adapt prior to being videotaped. While the ability of the individual animal to react to a new environment can not be ruled out entirely as a contributing factor to the differences in locomotor functions observed between young and aged rhesus monkeys, there is a growing body of data supporting that age-related decline in motor functions characterizing advancing age are more likely to result from deficits in basal ganglia functions in the central nervous system. Indeed, several alterations of the substantia nigra-striatum dopaminergic pathway are seen in both human senescence and in animal models of aging. These age-related changes include: loss of dopamine neurons in the substantia nigra, decreased tissue levels of nigro-striatal dopamine, and decreased levels of tyrosine hydroxylase and dopamine transporter markers [2,8,9,11,12,19,23]. In addition, changes in the functional dynamics of nigro-striatal dopamine release and regulation in the basal ganglia have been posited to contribute to age-related slowing of motor functions [12]. Along these lines, we have previously shown that glial cell-line derived neurotrophic factor (GDNF) administration in aged rhesus monkeys resulted in an increase in dopamine release in the substantia nigra, caudate nucleus and putamen, which was associated with an enhancement in motor functions in these animals [14]. Finally, there are changes in brain volume and composition; including striatal atrophy and elevations in iron levels in the basal ganglia during aging [1,15,16,26,28,30]. Considering that free, unconjugated, ferrous iron can be toxic to cells [20], it is also possible that age-related increases in striatal iron play a significant role in the motor deterioration observed during normal aging [16]. Thus, all or some of these variables could account for the motor abnormalities observed in aging in animals and humans. Further understanding of their relative contribution to the motor deficits seen with advancing age may help in the design of treatments that could ameliorate age-related declines in movement function.

In summary, EthoVision Pro has proven to be a useful tool for measuring age-related changes in locomotor activity in rhesus monkeys as they age from young adulthood. This technology could not only be used to help further our understanding of the mechanisms underlying aging, but also to study other neurodegenerative diseases such as Parkinson's disease where measurement of motor activity in animal models is necessary to determine the efficacy of experimental treatments [29]. In addition, EthoVision could also be useful in the clinical realm to conduct objective quantitative assessment of disease-related motor deficits such as bradykinesia and freezing commonly seen in parkinsonian patients.

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